

208.1009

jc997 U.S. PTO  
10/03/299  
10/25/01

**UNITED STATES PATENT & TRADEMARK OFFICE**

Re: Application of: LESLIE, Stewart Thomas  
Serial No.: To Be Assigned  
Filed: Herewith  
For: **TRANSDERMAL DOSAGE FORM**

**LETTER RE: PRIORITY**

Assistant Commissioner for Patents  
Washington, D.C. 20231

October 25, 2001

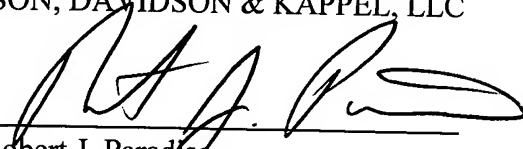
Sir:

Applicant hereby claims priority from British Patent Application No. 0026137.0 filed October 25, 2000.

Respectfully submitted,

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By

  
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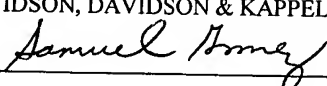
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Date of Deposit: October 25, 2001

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August 14, 2003

Examiner Micah-Paul Young  
United States Patent and Trademark Office  
Group Art Unit 1615  
Crystal Mall 1  
Alexandria, VA 22313

*15/ Priority  
Papers*

Re: U.S. Patent Application No. 10/037,299  
Entitled: **Transdermal Dosage Form**  
Our Ref.: 208.1009

Examiner Young:

As per your request, we have enclosed a copy of the priority document (GB 0026137.0) for the above-referenced case.

Please do not hesitate to contact us should you have any questions concerning this matter.

Very truly yours,  
DAVIDSON, DAVIDSON & KAPPEL, LLC

By: Richard V. Zanzalari  
Richard V. Zanzalari  
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cc: Clifford M. Davidson, Esq.



INVESTOR IN PEOPLE

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I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

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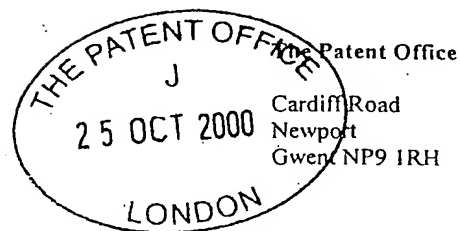
*Andrew Geraghty*

Dated

24 October 2001

**Request for grant of a patent**

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

1. Your reference **GBP83015**2. Patent application number  
(The Patent Office will fill in this part)**0026137.0**

3. Full name, address and postcode of the or of each applicant (underline all surnames)

Euro-Celtique S.A.  
122 Boulevard de la Petrusse  
L-2330 Luxembourg  
Luxembourg**25 OCT 2000**

Patents ADP number (if you know it)

**437319002** *IS*

If the applicant is a corporate body, give the country/state of its incorporation.

Luxembourg

4. Title of the invention **Transdermal Dosage Form**5. Name of your agent (if you have one)  
"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)Marks & Clerk  
57 - 60 Lincolns Inn Fields  
London WC2A 3LS

Patents ADP number (if you know it)

**18001**

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and (if you know it) the or each application number

Country

Priority application No  
(if you know it)Date of filing  
(day / month / year)

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application

Date of filing  
(day / month / year)

8. Is a statement of inventorship and of right to grant of a patent

**Yes**

required in support of this request? (Answer 'Yes' if:

- a) any applicant named in part 3 is not an inventor, or
  - b) there is an inventor who is not named as an applicant, or
  - c) any named applicant is a corporate body.
- See note (d))

Form 1/77

Indicate the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form 0

Description 4

Claim(s)

Abstract

Drawing(s)

10. If you are also filing any of the following, state how many against each item.

Priority documents

Translations of priority documents

Statement of inventorship and right to grant of a patent (Patents Form 7/77)

Request for preliminary examination and search (Patents Form 9/77)

Request for substantive examination (Patents Form 10/77)

Any other documents (please specify)

I/We request the grant of a patent on the basis of this application.

11.

Signature

*Marko & Clerk*

Date: 25 October 2000

12. Name and daytime telephone number of person to contact in the United Kingdom

GB Patent Filings  
0207 400 3000

## TRANSDERMAL DOSAGE FORM

The present invention relates to compositions for the percutaneous administration of opioid analgesics to the human body, and to percutaneous delivery systems such as transdermal patches incorporating such compositions.

Opioid analgesics are widely used in the treatment of moderate to severe pain, especially in terminal cancer or postoperative pain. The most widely used dosage forms of such opioid analgesics is tablet or injection. Tablets are the most favoured form because of ease of administration and convenience for domiciliary treatment. Controlled release tablets enabling once or twice a day dosing of for instance, morphine, oxycodone and hydromorphone are of increasing importance.

A number of proposals have been recently made for the administration of opioid analgesics by percutaneous absorption, using a so called transdermal patch.

Suggested opioid analgesics for this purpose are for instance, morphine, hydromorphone and buprenorphine, see for instance US Patent No. 5069 909, WO 94/10987, JP-A 2-191214.

One disadvantage common to all dosage forms of narcotic opioids is that of drug abuse. Most abusers, in order to obtain the desired effect of an 'high', usually require a large single dose of drug, normally by bolus injection. As a result of this techniques have been developed by abusers for the extraction of the active principle from the, usually, solid dosage form into aqueous and/or alcoholic solutions. However, because of the various excipients used in solid dosage forms this extraction is neither quick nor simple and serves to some degree as a disincentive.

The development of transdermal patches containing drugs which may be attractive to abusers gives rise to the problem of achieving formulations which will not be convenient to be used as source of the drug for the abuser. In some designs of transdermal patches the drug is provided in solution in a reservoir which might be simply extracted by a hypodermic needle; in other designs the drug may be provided in a gel which may also be susceptible to easy abstraction and then dissolution of the drug into an aqueous and/or alcoholic solution.

An aim of the present invention is to provide a solution to the foregoing problem by providing a composition for the percutaneous administration of an opioid analgesic, preferably a narcotic opioid analgesic, which includes the provision of a component susceptible to co-extraction with the opioid analgesic and which, when administered orally or by injection will distress the abuser.

According to one aspect of the present invention there is provided a composition for the percutaneous administration of an opioid analgesic, preferably a narcotic opioid analgesic, which comprises a therapeutic amount of the opioid analgesic in association with a vehicle or means for providing a transdermal flux of the opioid analgesic when

applied to a human body surface or membrane, and a quantity of a distressing substance which, when ingested orally or as parenteral bolus injection together with the opioid analgesic will produce a distressful reaction in the recipient.

By distressful reaction is meant a reaction such as vomiting, nausea, severe headache or other reaction that will tend to create an aversion to any further attempt to use a similar composition as a source of drug for abuse.

The distressing substance may be any substance which will achieve the distressful reaction when dosed orally, or by parenteral bolus injection in an amount which it is convenient to incorporate into a transdermal delivery device.

The distressing substance, may for example, be chosen from the classes of emetics, nauseants, and flavouring or bitter substances. Suitable substances are for instance chosen from ergolides and quaternary ammonium compounds. Among the substances which may be used are for examples ergolides such as bromocriptin, lisoline, pergolide, lysuride and their salts such as the maleates, non-permeant opioid antagonists such as derivatives of naloxone e.g. N-methyl-N-allyl naloxone or salts thereof, other opioid antagonists such as apomorphine or salts thereof, quaternary compounds such as bitter agents e.g. denatonium benzoate, and emetics such as Ipecacuanha and derivatives thereof. Other suitable substances include atropine or salts thereof.

The distressing substance, if it is non-permeant may be incorporated in the same vehicle as the opioid analgesic, and the vehicle may include a penetration enhancer.

In order to check whether the distressing substance is likely to be non-permeant the formulation can be tested in the donor phase in in vitro experiments employing a standard Franz cell arrangement with a suitable circulating recipient phase which may be buffered to e.g. pH 7.4 and a layer of human stratum corneum as barrier. The amount of drug and distressing substance which is absorbed through the barrier into the recipient phase can be observed by determination of the concentration in the recipient phase using HPLC testing of that phase. The test parameters can be readily optimised by the skilled person for the opioid analgesic which is being formulated and the test will then enable the selection of a distressing substance which is non-permeating under those conditions.

The opioid analgesic may be chosen from e.g., morphine, hydromorphone, buprenorphine, ketamine, fentanyl, tramadol or pharmaceutically acceptable, percutaneously transmissible salts thereof.

The compositions may incorporate the opioid analgesics in any vehicle conventionally used in transdermal compositions; thus it may, for example be dissolved in an aqueous and/or alcoholic solution, or incorporated in a suitable matrix including a pressure sensitive adhesive, and will usually include a penetration enhancer, or it may be incorporated in a material consisting substantially of penetration enhancer.

The composition will be incorporated in a transdermal device which may be of conventional form.

The device may, accordingly be an adhesive matrix type patch and comprise an impermeable backing layer, a matrix layer which contains the opioid analgesic and a penetration enhancer and distressing substance. The matrix layer may be a microporous material impregnated with the opioid analgesic, penetration enhancer and distressing substance. A variety of polymers which can be used as a microporous matrix are known and include a microporous polypropylene such as Celgard sold by Celanese Corp., Charlotte, N.C., USA, might be used.

Alternatively, the device may be of the reservoir type. Such devices are taught for example in US Patent Nos. 4379 454 and 4943 435. Devices of this type include an impermeable backing layer, an analgesic reservoir, a drug permeable membrane and an adhesive layer. In devices of this kind the distressing substance may be incorporated in the reservoir together with the opioid analgesic provided it is non-permeant through the drug permeable membrane, or is non-permeant through human skin.

Yet a further type of patch is a monolithic system in which a non-porous matrix is swollen with dissolved penetration enhancer, opioid analgesic and distressing agent. The choice of monolithic carrier or vehicle depends on the penetration enhancer and the materials which might be used are, for example acrylate and methacrylate copolymers. Monomers of these materials such as hydroxy ethyl methacrylate dissolved in a mixture of opioid analgesic, penetration enhancer and distressing agent can be polymerised by a suitable free radical polymerisation reaction to yield a cross-linked gel containing drug and enhancer.

Suitable transdermal devices, which may be modified in accordance with the present inventive concept include those described in for example EP-0 577 622, WO 87/06144, WO 94/02119 and US 5374645.

The amount of opioid analgesic included in a transdermal device according to the invention will depend upon the blood levels of the opioid which are desired for adequate analgesic effect, the transdermal flux and the desired duration of action of the device. The determination of these amounts are known from the literature or can readily be found by the skilled person.

The amount of distressing substance, to be incorporated in a transdermal device according to the invention, as indicated above, is determined by the requirement that it will be sufficient to cause distress to an abuser to whom it is administered orally or, as appropriate, by percutaneous bolus injection. For instance, in the case of the ergolides an amount in the range of 5-10mg or more may be suitable, in the case of lpecacuanha 0.1 to 2mg may be suitable and in the case of denatonium benzoate an amount of 0.1 to 2mg may be suitable. Suitable amounts of these components can be readily determined by suitable trials and experiments.



In preferred embodiments the distressing substance is chosen to be non-permeant either through a membrane which is permeable to the opioid analgesic or non-permeant through human skin. In other preferred embodiments of a transdermal device the distressing substance is separated from the opioid analgesic or is contained in a separate compartment, the location of the distressing agent, however being such that in order to remove the opioid analgesic from the device the distressing substance must also be released therewith.

In one preferred embodiment, a composition or device according to the invention contains buprenorphine or pharmaceutically acceptable salt thereof as the opioid analgesic and atropine or pharmaceutically acceptable salt thereof, or an ergolide or pharmaceutically acceptable salt thereof, as the distressing substance.